Neuroendocrine Alterations in Posttraumatic Stress Disorder

STEVEN M. SOUTHWICK, MD; RACHEL YEHUDA, PhD; and SHEILA WANG, PhD

Fear and life-threatening situations mobilize multiple brain regions, most notably the amygdala, hippocampus, locus coeruleus, and prefrontal cortex, in order to maximize chances for survival. Adrenergic, noradrenergic, dopaminergic, serotonergic, opiate, benzodiazepine, hypothalamic-pituitary-thyroid, and hypothalamic-pituitary-adrenal systems also become activated in response to danger. The simultaneous activation of numerous brain structures and neurochemical systems during acute stress prepares the organism to deal with potential threat in the short run but may have long-term negative consequences. It has been proposed that many symptoms of posttraumatic stress disorder (PTSD) are related to neurobiologic responses to stress that have become maladaptive.[1]

Although multiple neurochemical systems and brain structures are involved in acute and chronic responses to stress, investigations of humans with PTSD to date have focused largely on the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. In this review we primarily discuss these two systems. We also briefly discuss recent findings in the hypothalamic-pituitary-thyroid axis.

*Dr. **Southwick** is Professor of Psychiatry, Yale University School of Medicine, New Haven, Connecticut. **Dr. Yehuda** is Associate Professor of Psychiatry, Mt. Sinai School of Medicine, Bronx, New York. **Dr. Wang** is Associate Research Scientist, Yale University School of Medicine.*

***Address reprint requests to** Steven M. Southwick, MD, Professor of Psychiatry, Yale University School of Medicine, National Center for Posttraumatic Stress Disorder, VA CT Healthcare System, 950 Campbell Ave/116A, West Haven, CT 06516.*

SYMPATHETIC NERVOUS SYSTEM

The sympathetic nervous system (SNS) plays a critical role in the fight-flight response by increasing blood flow to muscles and vital organs, dilating pupils, limiting blood loss, and mobilizing energy for use by large muscle groups.[2,3] Since World War I, researchers and clinicians have suspected that "shell shock" was related to alterations in sympathetic nervous system activity as reflected by prominent symptoms of hyperarousal, vigilance, and agitation. In 1918 veterans with shell shock were exposed to laboratory sounds of gunfire and the smell of sulfuric flame and responded with greater increases in heart rate and respiratory rate than control subjects.[4] In the same year among a similar group of traumatized veterans, infusions of epinephrine were reported as causing exaggerated increases in heart rate, blood pressure, and subjective anxiety.[5] During World War II, Kardiner[6] emphasized the underlying neurobiologic nature of shell shock by coining the term *physioneurosis* to describe the physiologic hyperarousal resulting from severe psychological trauma. Similarly, Grinker and Spiegel[7] noted that traumatized combat veterans behaved "as if they had received an injection of adrenalin." To address this proposed overactivation of epinephrine, Crille[8] reported promising results in 152 veterans with neurocirculatory asthenia (the equivalent of PTSD) who were treated with bilateral denervation of the adrenal glands.

Over the past 40 years a large number of psychophysiology studies have reported heightened sympathetic nervous system activity in veterans with PTSD.[9] Although most studies have found no differences in resting baseline heart rate and blood pressure, the majority of studies have reported exaggerated increases in cardiovascular reactivity among subjects with PTSD compared with control subjects when

exposed to trauma-specific stimuli such as laboratory-simulated sights and sounds of combat or tape recordings of personally experienced traumas. Such exaggerated increases have not been reported in combat veterans without PTSD, in combat veterans with anxiety disorders other than PTSD, or in response to generic stressors (such as the film of an automobile accident) that have never been experienced by the trauma survivor.

To study the biochemical underpinnings of psychophysiologic hyperreactivity in PTSD, researchers have focused on the activity of catecholamines. Epinephrine, norepinephrine, and dopamine are each affected by stress and play an important role in responding to traumatic situations. These neurotransmitters facilitate a host of stress-related responses ranging from increased selective attention and cardiovascular activity to enhanced encoding and consolidation of long-term memory.

Twenty-Four Hour Urine Studies

Consistent with psychophysiologic observations, most studies of 24-hour urine epinephrine and norepinephrine excretion have shown significantly greater elevations in combat veterans with PTSD than in other groups of psychiatric patients.[10] When compared with levels in healthy controls, elevations have been reported for dopamine as well as epinephrine and norepinephrine. At least two studies, one in combat veterans with PTSD and the other in residents living within 5 miles of the Three Mile Island nuclear power plant, have suggested that alterations in norepinephrine may be a function of trauma rather than PTSD per se.

Resting Plasma Studies

Baseline catecholamine studies generally have found no significant differences between subjects with PTSD and healthy controls (for a review see reference 10). Exceptions include one study reporting significantly lower norepinephrine and one reporting significantly higher dopamine in combat veterans with PTSD. It is important to note that these studies typically used single-stick venipuncture, which may not provide an accurate baseline catecholamine measure because of the stress associated with the venipuncture itself. However, in a recent study in which consecutive plasma samples were drawn through an indwelling catheter every 30 minutes over a 24-hour circadian cycle, Yehuda and colleagues found significantly elevated levels in plasma norepinephrine (but not 3 methoxy-4-hydroxyphenylethylenegicol [MHPG] which is a major metabolite of norepinephrine) in combat veterans with PTSD but not in normal controls or in patients with major depression.[11]

Receptor Studies

Several studies have reported potential alterations at the adrenergic receptor level and at sites distal to the receptor.[10] In one radioligand receptor binding study, significantly fewer alpha-2 adrenergic receptors were found on the surface of platelets among combat veterans with PTSD than among controls. Similar findings were reported among a group of traumatized children with PTSD. Reduced platelet alpha-2 adrenergic receptor numbers have also been seen in patients with congestive heart failure and hypertension, conditions characterized by excessive catecholamine secretion. It has been suggested that decreased receptor numbers are caused by chronic elevation of circulating catecholamines.

Many symptoms of PTSD may be related to neurobiologic responses to stress that have become maladaptive.

In separate studies, lower levels of basal cAMP and basal adenylate cyclase have been found in patients with PTSD compared with controls. Furthermore, lower responsiveness to isoproterenal and forskolin stimulation has been reported in patients with PTSD. It has been suggested that these findings reflect a diminished responsivity of the receptor adenylate-cyclase complex.

Challenge studies

Challenge studies are designed to provoke biological systems under controlled conditions allowing for an assessment of system responsivity. In PTSD, sympathetic nervous system responsivity has been assessed using nontrauma-related stressors, trauma-related stressors, and neuroendocrine challenges.

In one non-trauma related challenge study, McFall and colleagues[12] reported no differences in heart rate, blood pressure, plasma epinephrine, and norepinephrine among combat veterans compared with controls while viewing a film depicting an automobile accident. On the other hand, Hamner and colleagues[13] found that combat veterans with PTSD had significantly greater increases in plasma MHPG in response to vigorous physical exercise on a treadmill compared with controls. However, there were no differences in maximal blood pressure and heart rate response and in pre- and post-test plasma norepinephrine levels.

Stress-induced psychophysiologic and catecholamine responses have been measured in parallel during laboratory exposure to trauma-related stimuli. McFall and colleagues[12] found higher levels and a parallel rise in subjective distress, blood pressure, heart rate, and plasma epinephrine among combat veterans with PTSD than in controls both during and after the view-

Indeed [in Munck's view], if the body's stress responses were not restrained by cortisol, the responses that cause short-term benefits . . . would ultimately produce long-term damage.

ing of a combat film. In a similar study, Blanchard and colleagues[14] reported significantly greater increases in heart rate and plasma norepinephrine among combat veterans with PTSD than in combat veterans without PTSD.

Three relevant neuroendocrine challenge studies have included the use of desipramine, lactate, and yohimbine as probes of catecholamine function. To assess postsynaptic alpha-2 adrenergic receptor function, Dinan and colleagues[15] measured growth hormone levels in response to desipramine. No differences were found between traumatized subjects and controls. Lactate is known to induce panic attacks in patients with panic disorder. In subjects with PTSD, it also has been shown to induce panic attacks as well as flashbacks in a high percentage of subjects.[16] Central noradrenergic stimulation has been hypothesized as a potential mechanism for the observed exaggerated reactivity in both panic disorder and PTSD patients. In two separate studies, yohimbine, an alpha-2 adrenergic receptor antagonist that activates noradrenergic neurons by blocking the alpha-2 autoreceptor, has resulted in pronounced behavioral, cardiovascular, and biochemical responses among subjects with PTSD but not in healthy controls. For example, in one double blind placebo controlled study of 20 Vietnam veterans with PTSD and 18 healthy controls, 70% of veterans had a panic attack and 40% a flashback in response to yohimbine.[17] There were no yohimbine-induced panic attacks or flashbacks in the control group. Abnormal presynaptic noradrenergic reactivity was suggested by a more than twofold greater elevation of plasma MHPG among the PTSD patients.

SUMMARY OF SYMPATHETIC NERVOUS SYSTEM FINDINGS IN PTSD

Taken together, the data point to an increased sensitivity of the sympathetic nervous system that is most clearly evident under conditions of stress. This stress-related reactivity has been reported in psychophysiologic and neuroendocrine challenge studies. It has been suggested that inconsistencies between single plasma samples and 24-hour urine studies may be explained by phasic increases in catecholamine reactivity in response to meaningful stimuli that are picked up during sampling over a 24-hour period but not in studies that measure catecholamines at a single point in time when the subject is resting.[10,18]

HYPOTHALAMIC PITUITARY ADRENAL AXIS

Under conditions of stress, the hypothalamus releases corticotropin-releasing factor (CRF), which then stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH in turn stimulates the adrenal gland to release cortisol. In the 1980s Munck and colleagues theorized that the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis worked in tandem. Whereas catecholamines were known to facilitate the availability of energy to the body's vital organs, it was hypothesized that cortisol's role was to shut down sympathetic activation following stress. Cortisol's other role was to suppress the HPA axis via negative feedback inhibition on the pituitary, hypothalamus, and other sites. Ultimately this negative feedback inhibition lead to the restoration of basal hormone levels. In Munck's view, cortisol was more an anti-stress hormone than a stress hormone. Indeed if the body's stress responses were not restrained by cortisol, the responses that cause short-term benefits in the acute aftermath of stress would ultimately produce long-term damage.[19]

Cortisol Levels in the Acute Aftermath of Trauma

Over six decades of animal and human research has consistently demonstrated a positive linear relationship between severity of stressor and degree of cortisol release. However, two recent studies have suggested that this may not be the case in trauma survivors who develop PTSD. McFarlane and colleagues found plasma cortisol levels in the immediate aftermath of an automobile accident to be lower in survivors who went on to develop PTSD than in those who did not develop PTSD.[20] A second study demonstrated that low cortisol at the time of rape was associated with the subsequent development of PTSD and with a past history of rape.[21] These two longitudinal studies suggest that the acute cortisol response to trauma in survivors who develop PTSD may differ from the response seen in individuals who do not develop PTSD. The findings do not preclude the possibility that individuals with an attenuated response may have had lower basal levels of cortisol before the traumatic event.

Twenty-Four Hour Urine Studies

Most 24-hour urine studies of cortisol excretion in trauma survivors with PTSD also have found unexpectedly low levels. In 1986 Mason and colleagues reported lower 24-hour urinary cortisol excretion in nine combat veterans with PTSD than in four other patient groups with separate psychiatric diagnoses. Similarly, in two separate studies, Yehuda and colleagues found lower urinary cortisol in PTSD patients than in subjects with major depression, panic disorder,

bipolar mania, and schizophrenia, and lower excretion in inpatient and outpatient combat veterans with PTSD than in healthy controls. Finally, a more recent study has demonstrated significantly lower urinary cortisol levels in Holocaust survivors with PTSD than in Holocaust survivors without PTSD and compared with a demographically similar group of non-traumatized individuals. In contrast to these findings, Pitman and Orr reported higher 24-hour urine cortisol excretion in combat veterans with PTSD compared with combat veterans without PTSD, and Lemieux and Coe found increased levels in adult women who had developed PTSD from childhood sexual abuse. Potential reasons for discrepancies in 24-hour urine studies include differences in body weight, technique of sample collection, and storage as well as assay methodology.

Twenty-Four Hour Plasma Cortisol

Although 24-hour urine studies provide a quantitative assessment of overall cortisol output, they do not delineate the pattern of cortisol levels over the course of the diurnal cycle. In a recent investigation comparing patients with PTSD with normal controls and patients with major depression, Yehuda and colleagues[23] found a pattern of significantly lower cortisol in the late evening and early morning in the PTSD group. However, there was no difference in peak cortisol level between the normal and PTSD groups. The results suggest differences in the patterning of cortisol release and regulatory influences controlling cortisol release among patients with PTSD, patients with major depression, and healthy controls.

Receptor Studies

Like norepinephrine, cortisol binds to receptors to exert its physiological effect. In three separate studies of combat veterans with PTSD and in one study of adult women with PTSD secondary to childhood physical and sexual abuse, subjects with PTSD have been shown to have a greater number of lymphocyte glucocorticoid receptors than normal controls or comparison groups of patients with major depression, panic disorder, bipolar mania, or schizophrenia. (For a review see reference 22.) A greater number of glucocorticoid receptors is consistent with an upregulation in response to low circulating levels of cortisol. However, it is also possible that an increased number of glucocorticoid receptors is a primary alteration in PTSD, exerting an increase in negative feedback at the level of the hypothalamus and pituitary with a resultant decrease in ACTH and circulating cortisol.

Neuroendocrine Challenge Studies

CRF is believed to play an important role in the stress response through its effects on the HPA axis and on extrahypothalamic brain structures such as the amygdala and locus coeruleus, which are known to be critically involved in the organism's capacity to deal with threatening situations.

Results suggest differences in the patterning of cortisol release and regulatory influences among patients with PTSD, patients with major depression, and healthy controls.

Two studies of the ACTH response to CRF also provide indirect evidence for increased CRF release in individuals with PTSD. One study of combat veterans with PTSD[24] and one study of sexually abused girls[25] reported a blunted ACTH response to exogenous CRF. Blunting of the ACTH and cortisol response to CRF is consistent with downregulation of pituitary CRF receptors secondary to chronic hypothalamic CRF hypersecretion.

One additional finding that supports CRF hypersecretion in PTSD involves the use of metyrapone to block the conversion of 11-deoxycortisol to cortisol. By blocking cortisol synthesis, the confounding effects of negative feedback and differing ambient cortisol levels on glucocorticoid receptor responsiveness is virtually eliminated, allowing for a more direct measure of pituitary release of ACTH. In healthy subjects, the abrupt discontinuation of cortisol synthesis normally results in a two- to fourfold increase in plasma ACTH within a period of several hours. In one study of eleven combat veterans with PTSD, the PTSD group had significantly greater increases in ACTH and 11-deoxycortisol than the healthy control group.[26]

In addition to the above evidence for CRF hypersecretion, challenge studies also provide indirect evidence for increased glucocorticoid-mediated negative feedback in traumatized individuals with PTSD. When the synthetic glucocorticoid dexamethasone is administered to healthy controls, it increases negative feedback at the level of the hypothalamus and pituitary by stimulating glucocorticoid receptors, with a resultant decrease in the release of CRH, ACTH, and, ultimately, endogenous cortisol from the adrenal gland. In five separate published studies, it recently has been reported that dexamethasone has an exaggerated effect in subjects with PTSD compared with in healthy controls. (For a review see reference 22.) Exaggerated cortisol suppression has been reported in adults whose PTSD was caused by childhood sexual abuse, the Vietnam war, or the Persian Gulf war and in children with PTSD secondary to the Armenian earthquake. Of note, most studies have reported a very different response in subjects who have major depression but not PTSD.

In 1927, Bram reported that a clear history of traumatic stress was found in 85% of more than 3000 patients with thyrotoxicosis.

Cerebral Spinal Fluid

Consistent with the above studies, Bremner and colleagues[27] reported significantly elevated cerebrospinal fluid (CSF) concentrations of CRF among 11 combat veterans with PTSD compared with 17 healthy comparison subjects. These differences remained significant after covariance for age. Elevated CSF CRF supports the hypothesis that PTSD involves a hypersecretion of neuronal CRF. In pre-clinical studies, intraventricular administration of CRF leads to fear and anxiety-related behaviors, potentiation of acoustic startle, increased firing of the locus ceruleus (the site of most noradrenergic cell bodies in the brain), increased plasma epinephrine and norepinephrine concentrations, and increased attention and arousal.

Summary of HPA axis findings in PTSD

The finding of low cortisol in subjects with PTSD was initially surprising because of the well known association between high cortisol levels and stress. However, on further examination it has become clear that lower cortisol levels in PTSD are a downstream effect that likely results from an increased negative feedback inhibition, possibly secondary to increases in the sensitivity of glucocorticoid receptors. This means that the HPA axis in PTSD may actually be more dynamic and responsive—an idea that is compatible with theories of biological sensitization. It may be that certain aspects of HPA axis alterations observed in PTSD reflect the presence of risk factors that determine how an individual will respond to a traumatic event. Future research is needed to clarify this issue.

HYPOTHALAMIC PITUITARY THYROID AXIS

Biological studies of traumatic stress in humans to date have focused mainly on the responses of the sympathetic-adrenal medullary axis and catecholamines and the hypothalamic-pituitary adrenal axis and cortisol. Less attention has been given to the hypothalamic pituitary thyroid axis, though the evidence of an important relationship between traumatic stress and thyroid function has a long history.[28] The original clinical report of hyperthyroidism by Parry in 1825 described the onset of symptoms in a woman 4 months after a terrifying experience in which she was accidentally thrown down the stairs in a wheelchair. In 1927, Bram reported that a clear history of traumatic stress was found in 85% of more than 3000 cases of thyrotoxicosis. The most striking common feature associated with the stressful experiences appeared to be extreme fear concerning biologic survival. Recent research continues to support the observation that more patients with hyperthyroidism give a history of traumatic stress than do members of a control population.

Serum Thyroid Studies in Combat-Related PTSD

In a series of thyroid studies, Mason and colleagues reported an unusual thyroid profile in Vietnam veterans with combat-related PTSD compared with controls. These findings were reported in four groups of 24 (N=96) Vietnam combat veterans.[29] The T3 elevations were replicated in a group of Israeli combat veterans (n=11)[30] and a group of World War II combat veterans (n=12)[31] with PTSD. Mason and colleagues hypothesized that since about 80% of the body's supply of T3 is produced by peripheral conversion of free T4 to T3, the T3 elevations found in these combat veterans might reflect increased peripheral conversion. The conversion of T4 to T3 can be augmented by catecholamines, which consistently have been found to be elevated in this population. The T3 elevations observed did not for the most part exceed the "normal range," as specified for the diagnosis of glandular disease in the field of clinical endocrinology, but evidence supports the observation that relatively modest changes in thyroid hormone levels may have important clinical significance in relation to psychiatric disorders.

Clinical Significance of T3 Elevations in Combat-Related PTSD

Many symptoms of hyperthyroidism are similar to hyperarousal symptoms observed in PTSD; these include irritability, difficulty sleeping, difficulty concentrating, anger outbursts, and exaggerated startle. Since T3 is two to four times more biologically active than T4, it is not surprising that T3 elevations have been linked to PTSD symptoms, specifically hyperarousal symptoms, in combat veterans. T3 has also been found to be positively correlated with novelty seeking measured by the Cloninger Tridimensional Personality Questionnaire.

Thyrotropin-Releasing Hormone Challenge Studies

In a study comparing combat veterans with PTSD, depressed patients and controls, Kosten and colleagues reported blunted thyrotropin (TSH) responses to thyrotropin-releasing hormone (TRH) infusion in 67% of the depressed patients, 27% of the PTSD patients and 28% of the control subjects. Rather than blunting, 36% of the PTSD patients and only 10% of the control and depressed patients had augmented TSH responses, further suggesting alterations in the hypothalamic-pituitary-thyroid axis in this population.

Summary of Thyroid Findings in PTSD

There is strong evidence indicating that veterans with PTSD from combat stress show altered thyroid profiles, specifically elevations of T3, which appear to be related to PTSD symptoms, especially hyperarousal.

NEUROBIOLOGIC MODELS OF PTSD

To explain many of the above findings, a number of neurobiologic models for PTSD have been offered in recent years.[33-38] Several commonly cited models include stress sensitization, fear conditioning, and enhanced encoding and consolidation of memory for traumatic events. Learned helplessness has also been proposed as a model for both depression and PTSD.

Stress sensitization refers to a stressor-induced increase in behavioral, physiologic, and biochemical responding to subsequent stressors of the same or lesser magnitude. Significantly greater behavioral, cardiovascular, and biochemical responses to equivalent doses of yohimbine in combat veterans with PTSD compared with healthy controls is an example of evidence supporting a stress sensitization model. It has been proposed that multiple neurobiologic systems, including catecholamine systems and the HPA axis, can become sensitized over time by traumatic stress and as a result contribute to PTSD symptoms such as hypervigilance, poor concentration, insomnia, exaggerated startle response and intrusive memories.

Fear conditioning involves the pairing of a fear-provoking aversive stimulus or event with a neutral stimulus. As a result of this association, the neutral stimulus, in the absence of the original fear-provoking stimulus, acquires the capacity to induce fear. For example, smells or sounds that were previously neutral, like the smell of diesel fuel or the sound of a helicopter, can become fear-conditioned stimuli if present during a traumatic event. These fear conditioned stimuli can, by themselves, induce fear-related neuroendocrine and behavioral responses. Fear conditioning can occur very rapidly and last for long periods of time. Furthermore, it can occur outside of conscious awareness. Support for a fear conditioned model of PTSD comes from psychophysiologic studies showing physiologic hyperreactivity to stimuli associated with the original trauma but not for non-specific stressors.

Animal and human studies suggest that arousing or emotionally exciting events are remembered better than emotionally neutral events. It has been proposed that this facilitation of memory is caused by endogenous neuromodulators, such as epinephrine and norepinephrine, that are released during arousing and stressful circumstances. Pitman has postulated that overstimulation of these stress-related neuromodulators during traumatic events causes overconsolidated and deeply engraved memories for the event. These overconsolidated memories would then contribute to the intrusive recollections that are characteristic of PTSD.

Recent research continues to support the observation that more patients with hyperthyroidism give a history of traumatic stress than do controls.

Hereditary and developmental factors undoubtedly play a key role in fear-related behaviors, the stress response and post-trauma symptom development. From family history and twin study data, it has been estimated that between 13% and 34% of the variance for specific PTSD symptom clusters is genetically transmitted.[39] It is possible that inherited variations in the capacity for fear-conditioning, sensitization, and memory consolidation help to determine who is likely to develop PTSD. From a developmental standpoint it has been proposed that psychological trauma in childhood may differentially affect maturation of various brain regions, particularly those regions involved in fear and alarm.

Not all individuals who are exposed to DSM-IV criterion A stressors develop PTSD. A variety of social, psychological, and neurobiologic factors play a role in determining individual susceptibility. As more is learned about the underlying neurobiologic pathophysiology of PTSD and its relationship to psychosocial risk factors, it should be possible to develop more effective strategies for the treatment and even prevention of this often devastating disorder.

REFERENCES

1. Charney DS, Deutch AY, Krystal JH, et al. Psychobiologic mechanisms of posttraumatic stress disorder. *Arch Gen Psychiatry.* 1993;50:294-305.
2. Cannon WB. Emergency function of adrenal medulla in pain and the major emotions. *Am J Physiology.* 1914;3:356-372.
3. Mountcastle ZB. *Medical Physiology, 13th Ed.* St. Louis, Mosbey Publishing:1973.
4. Meakins JC, Wilson RM. The effect of certain sensory stimulation on the respiratory rate in cases of so-called "irritable heart". *Heart.* 1918;7:17-22.
5. Fraser F, Wilson EM. The sympathetic nervous system and the "irritable heart of soldiers." *British Med J.* 1918;2:27-29.
6. Kardiner A, Spiegel H. *The Traumatic Neuroses of War.* New York, Paul Hoeber: 1947.
7. Grinker RR, Spiegel JP. *Men Under Stress.* Philadelphia, Blakiston: 1945.
8. Crille G. Results of 152 denervations of the adrenal glands in the treatment of neurocirculatory asthenia. *Military Surgeon* 1945;87:509-513.
9. Prins A, Kaloupek DG, Keane TM. Psychophysiological evidence for autonomic arousal and startle in traumatized adult populations, in MJ Friedman, DS Charney & AY Deutch (eds.) *Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to Post-Traumatic Stress Disorder.* Philadelphia, Lippincott-Raven: 1995.
10. Southwick SM, Yehuda R, Morgan CA. Clinical studies of neurotransmitter alterations in post-traumatic stress

disorder, in MJFriedman, DS Charney & AY Deutch (eds.) *Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to Post-Traumatic Stress Disorder*. Philadelphia PA, Lippincott-Raven Company: 1995.
11. Yehuda R, Siever LJ, Teicher MH, Levengood RA, Gerber DK, Schmeidler J, et al. Plasma norepinephrine and MHPG concentrations and severity of depression in combat PTSD and major depressive disorder. *Biol Psychiatry* (In Press).
12. McFall ME, Vaith RC, Murburg MM. Basal sympathoadrenal function in post traumatic stress disorder. *Biol Psychiatry*. 1992;31:1050-1056.
13. Hamner MB, Diamond BI, Hitri A. Plasma norepinephrine and MHPG responses to exercise stress in PTSD. In M. Murburg (ed.), *Catecholamine Function in Posttraumatic Stress Disorder: Emerging Concepts, Progress in Psychiatry*, Series #42. Washington, DC, American Psychiatric Press.
14. Blanchard EB, Kolb LC, Prins A, et al. Changes in plasma norepinephrine to combat-related stimuli among Vietnam Veterans with post traumatic stress disorder. *J Nerv Ment Dis*. 1991;179:371-373.
15. Dinan TG, Barry S, Yatham LN, et al. A pilot study of a neuroendocrine test battery. In posttraumatic stress disorder. *Biol Psychiatry*. 1991;28:665-672.
16. Rainey JM, Aleem A, Ortiz A, et al. A laboratory procedure for the induction of flashbacks. *Am J Psychiatry*. 1987;144:1317-1319.
17. Southwick SM, Krystal JH, Morgan CA, et al. Abnormal noradrenergic function in posttraumatic stress disorder. *Arch Gen Psychiatry*. 1993;50:266-274.
18. Murburg MM: *Catecholamine Function in Posttraumtic Stress Disorder: Emerging Concepts, Progress in Psychiatry*, Series #42. Washington DC; American Psychiatric Press: 1994.
19. Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocrine Reviews*. 1984;93:9779-9783.
20. McFarlane AC, Atchison M, Yehuda R. The acute stress response following motor vehicle accidents and its relation to PTSD. In Yehuda R, McFarlane AC (eds.) *Psychobiology of Posttraumatic Stress Disorder*. New York, NY: New York Academy of Sciences: 1997.
21. Resnick HS, Yehuda R, Pitman RK, Foy DW. Effect of previous trauma on acute plasma cortisol level following rape. *Am J Psychiatry*. 1995;152:1675-1677.
22. Yehuda R. Sensitization of the hypothalamic-pituitary-adrenal axis in posttraumatic stress disorder. In Yehuda R, McFarlane AC (eds.) *Psychobiology of Posttraumatic Stress Disorder*. New York, NY: New York Academy of Sciences: 1997.
23. Yehuda R, Teicher MH, Trestman RL, et al. Cortisol regulation in posttraumatic stress disorder and major depression: A chronological analysis. *Biol Psychiatry*. 1996;40:79-88.
24. Smith MA, Davidson S, Ritchie JC, et al. The corticotropin-releasing horomone test in patients with PTSD. *Biol Psychiatry*. 1989;26:349-355.
25. De Bellis MD, Chrousos GP, Dorn LD, et al. Hypothalimic-pituitary-adrenal axis dysregulation in sexually abused girls. *J Clin Endocrinol Metab*. 1994;78:249-255.
26. Yehuda R, Levengood RA, Wilson S, et al. Increased pituitary activation following metyrapone administration in post-traumatic stress disorder. *J Psychoneuroendo*. 1996;21:1-16.
27. Bremner JD, Licinio J, Darnell A, et al. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. *Am J Psychiatry*. 1997;154: 624-629.
28. Mason J, Wang S, Southwick S, et al. Some approaches to the study of clinical implications of thyroid alterations in posttraumatic stress disorder. In Friedman MJ, Charney DS, Deutch AY (eds.) *Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to Post-Traumatic Stress Disorder*. Philadelphia; Lippincott-Raven: 1995.
29. Mason J, Southwick S, Yehuda R, et al. Elevation of serum free triiodothyronine, total triiodothyronine, thyroxine-binding globulin, and total thyroxine levels in combat-related posttraumatic stress disorder. *Arch Gen Psychiatry*. 1994;51:629-641.
30. Mason J, Weizman R, Laor N, et al. Serum triiodothyronine elevation in Israeli combat Veterans with posttraumatic stress disorder: a cross cultural study. *Biol Psychiatry*. 1996:39:835-838.
31. Wang S, Mason JW. Elevations of serum T3 levels and their association with symptoms in WWII veterans with combat-related posttraumatic stress disorder: Replication of findings in Vietnam combat veterans. *Psychosom Med* (submitted).
32. Kosten TR, Wahby VS, Giller EL et al. The dexamethasone suppression test and TRH-stimulation test in posttraumatic stress disorder. *Biol Psychiatry*. 1990;28: 657-664.
33. Rasmusson, AM, Charney D. Animal models of relevance to PTSD. In Yehuda R, McFarlane AC (eds.) *Psychobiology of Posttraumatic Stress Disorder*. New York, NY: New York Academy of Sciences: 1997.
34. McGaugh JL. Significance and remembrance: The role of neuromodulatory systems. *Psychol Sci*. 1990;1:15-25.
35. Pitman RK. Posttraumatic stress disorder horomones, and memory. *Biol Psychiatry*. 1989;26:221-223.
36. LeDoux J. *The Emotional Brain: The Mysterious Underpinnings of Emotional Life*. New York, NY; Simon & Schuster: 1996.
37. Southwick SM, Bremner JD, Krystal JK, et al. Psychobiologic research in Post Traumatic Stress Disorder. *Psychiatr Clin North Am*. 1994;17:251-264.
38. Post RM, Weiss SRB, Smith MA. Sensitization and kindling. In Friedman MJ, Charney DS, Deutch AY (eds.) *Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to Post-Traumatic Stress Disorder*. Philadelphia, Lippincott-Raven: 1995.
39. True W, Rice J, Eisen S, et al. A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. *Arch Gen Psychiatry*. 1993;50:257-264.